biotinylating the scTCR in accordance with standard methods, followed by cross-linking the molecule after strepavidin addition. Biotin-streptavidin conjugation produces the polyvalent scTCR fusion protein, typically in a tetrameric format.

Polyvalent scTCR fusion proteins can also be made by covalently linking the fusion protein to latex beads (Polysciences, Inc. Warrington, PA) in accordance with known methods (see e.g., Newman, S.L. et al. *J. Immunol.* (1995) 154, 753). For example, scTCR fusion proteins can be directly coupled to the beads through either amine groups or disulfide groups. Denaturation of the scTCR can be minimized by coating the latex bead with either strepavidin or an antibody which specifically binds the scTCR. For example, the EE-tag antibody can be used to coat the latex bead in cases where the scTCR includes an EE-tag as described above.

Example 10 - Effects of scTCR Fusion Protein on Antigen Stimulated T cell Proliferation *in vitro*

The soluble fusion proteins made in the examples above can be tested for capacity to suppress antigen stimulated T cell proliferation. Examples of such tests are those disclosed in said published PCT Application No. US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387.

In one method disclosed in said published PCT Application No. US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387, T cells can be isolated from any mammals such as mice. For example, OVA-primed T cells can be obtained from BALB/c mice (MHC Class II: I-Ad) by immunizing with 50 μg of OVA 323-339-KLH in complete Freund's adjuvant, subcutaneously at the base of the tail (see Harlow and Lane, *supra*). For example, two immunizations can be performed at 7 day intervals and, one week after the second injection, mice can be sacrificed and the inguinal and parasitic lymph nodes removed and dispersed into a single cell suspension. Subsequently, the single cell suspension can be depleted of antigen presenting cells by incubation on nylon wool and Sephadex G-10 columns. The purified T cell populations can be further incubated either with Click's medium alone, or with scTCR fusion proteins dissolved in Click's medium.

Activated B cells from BALB/c mice can be used as antigen presenting cells in a conventional B cell proliferation assay. For example, B cells can be prepared by culturing spleen cells with 50 μg/ml of LPS (ie. liposaccharides) for 48 to 72 hours at which time activated cells can be isolated by density gradient centrifugation on Ficoll/Hypaque (Pharmacia). Activated B cells can then be pulsed with the OVA 323-339 peptide for 3 hours, washed extensively, fixed with paraformaldehyde to inhibit proliferation of B cells, and added to purified T cells alone or T cells plus soluble scTCR fusion proteins. See generally *Selected Methods in Cellular Immunol.* (1980) B.B. Mishell and S.M. Hiigi W.H. Freeman and Co. San Francisco.

A standard B cell proliferation assay can be carried out in 96 well round bottom microtiter plates at 37°C, 5% CO2 for 3-5 days. Wells can be pulsed with WST-1 (Boehringer Mannheim) reagent for 4 hours prior to termination of cultures. The optical density of the cultures can then be recorded. The degree of peptide-reactive T cell proliferation will be indicative of the T_H cell responses (i.e. clonal expansion) that took place in the mice following immunization.

Example 11 - Effects of scTCR Fusion Proteins on Antigen Stimulated T cell Proliferation *in vivo*

The soluble fusion proteins can be further tested for inhibition of T cell clonal expansion *in vivo* in accordance with methods disclosed previously in said published PCT Application No. US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387.

For example, three test groups can be set up as follows: 15 BALB/c mice can be injected intraperitoneally (IP) with approximately 10 to 100 μg of OVA 323-339-KLH conjugate in Complete Freund's adjuvant to induce an immune response to the OVA 323-339 peptide. On the day before immunization and 2 days after immunization with OVA-KLH, 5 of the mice can be injected IP with approximately 10 to 100 μg of the anti-OVA/I-Ad scTCR fusion protein in PBS. The scTCR will bind to the I-Ad/OVA MHC Class II molecules to reduce or eliminate TCR molecules on antigen-specific T cells from engaging I-Ad/OVA molecules on APCs. The remaining 10 mice can be used as controls. For example, 5 of the mice can receive PBS and the other 5 can receive a scTCR with a different specificity. The mice can be sacrificed 10 days after immunization. The lymph nodes can be removed

and dispersed into a single cell suspension. The suspension can be depleted of antigen presenting cells by incubation on nylon wool and Sephadex G-10 columns.

The resulting purified T cell populations can be incubated with APCs pulsed with the OVA 323-339 peptide. Activated B cells from BALB/c mice can be used as APCs in the proliferation assay. The B cells can be prepared by culturing mouse spleen cells with 50 μg/ml of LPS for 48 to 72 hours at which time activated cells can be isolated by density gradient centrifugation on Lymphoprep. Activated B cells can then be pulsed with the OVA 323-339 peptide for 3 hours, washed extensively, fixed with paraformaldehyde to inhibit proliferation of B cells, and added to purified T cells.

The T cell proliferation assay can be carried out in 96 well round bottom microtiter plates at 37°C, 5% CO2 for 3-5 days. Wells can be pulsed with WST-1 reagent for 4 hours prior to termination of cultures and then read at different absorbencies. The degree of peptide-reactive T cell proliferation in this assay will be indicative of the T_h cell response (ie. clonal expansion) that took place in the mice following immunization. It is expected that co-injection of the scTCR fusion proteins with either the OVA-KLH or the HSV-KLH immunization will limit the amount of clonal expansion and subsequent *in vitro* proliferation of the OVA-reactive T cell lines without affecting expansion of the HSV-reactive T cell lines.

Example 12 - Suppression of a Murine Autoimmune Disease

Experimental allergic encephalomyelitis (EAE) is a murine autoimmune disease that is generally recognized to be an animal model for multiple sclerosis. Encephalitogenic regions of two proteins, myelin basic protein (MBP amino acids 91-103) and proteolipoprotein (PLP amino acids 139-151) have been defined. See generally Martin, R. et al. *Ann. Rev. Immunol.* (1992) 10:153.

In the SJL mouse strain, EAE can be induced to develop following immunization with the encephalitogenic peptide or adoptive transfer of MBP-reactive T cells. To determine whether treatment with soluble anti-MBP 91-103 or anti-PLP 139-151 T cell receptors will prevent EAE development after T cell activation, SJL mice can be injected with MBP 91-103 and PLP 139-151 reactive T cell blasts *in vivo*. Suitable assays to detect T cell expansion in such mice have been disclosed in said published PCT Application No.

US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387.

As further disclosed in said published PCT Application No. US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387, EAE can be induced in SJL mice by immunization with approximately 400 μg of MBP 91-103 in complete Freund's adjuvant on the dorsum. Ten to 14 days later, regional draining lymph node cells can be harvested as described above and cultured in 24-well plates at a concentration of $6x10^6$ cells per well in 1.5 ml of RPMI 1640 medium/10% fetal bovine serum/1% penicillin/strepomycin/MBP at 50 μg/ml. After a 4 day *in vitro* stimulation, MBP 91-103 reactive T cell blasts can be harvested via a Ficoll/Hypaque density gradient (Pharmacia), washed twice in PBS, and $1.3x10^7$ cells can be injected into each mouse.

Mice which receive encephalitogenic MBP 91-103 reactive T cells can be further injected with approximately 100 μg of an scTCR fusion protein specific for MBP 91-103 (IAs context), 100 μg of an scTCR fusion protein specific for the PLP 139-151 (negative control), or saline (sham control) on day 0, 3, and 7 i.v. (total dose 300 μg). Clinical and histological evaluation can be performed to confirm that the scTCR molecule reactive to MBP 91-103 + IAs inhibited the development of EAE in the mice.

As further disclosed in said published PCT Application No. published PCT/US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387, to induce EAE in SJL mice with PLP peptide 139-151, the mice can be immunized with PLP peptide 139-151 dissolved in PBS and mixed with complete Freund's adjuvant containing Mycobacterium tuberculosis H37Ra at 4 mg/ml in a 1:1 ratio. Mice can then be injected with 152 μg of peptide adjuvant mixture. On the same day and 48 hrs later, all animals can be given 400 ng of pertussis toxin. Adoptive transfer of EAE is then performed as described above.

In accordance with methods described above (see Example 1), TCR DNA can be obtained from normal and EAE diseased SJC mice. The TCR DNA can then be used to construct scTCRs which can be ligated into suitable DNA vectors comprising a bacteriophage coat protein or suitable fragment thereof. The PLP or MBP reactive scTCR peptide fusions can then be expressed and purified if desired in accordance with the above examples.

The scTCR peptide fusion proteins can then be tested for the capacity to prevent development of EAE.

As described below in Examples 14 and 15 which follow, the PLP and MBP scTCR fusion proteins can be used to make a bacteriophage display library. The scTCR bacteriophage display library can be screened for receptors that can bind to either the MBP (91-103) or PLP (139-151) peptide in association with IA^s. As described more fully below in Examples 15, bound scTCR fusion proteins can be isolated by suitable panning techniques. The scTCR fusion proteins thus obtained can be used for production of soluble scTCR fusion proteins which can then be evaluated for blocking autoreactive T cells in SJL mice.

Example 13 - Affinity Maturation of scTCR antigen binding domains

It is expected that high affinity scTCR fusion proteins can reduce or eliminate undesirable interactions between TCRs and MHC/peptide complexes such as those occurring in autoimmune disorders, allergies, and transplantation rejection. A high affinity scTCR fusion protein can be used, e.g., as a competitor for the corresponding native TCR, thereby reducing or eliminating binding between T cells bearing the TCR and APCs bearing MHC/peptide molecules. Alternatively, the scTCR molecule can reduce binding to a superantigen. It is believed that the low binding affinity and rapid off-rate associated with native TCRs will allow many scTCR fusion proteins to interact with a single MHC/peptide molecule.

High affinity scTCR fusion proteins can be used to reduce or eliminate binding of MHC/peptide molecules which activate autoreactive T cells. To accomplish this, genetic engineering (e.g., site directed or linker scanning mutagenesis) can be used to improve the affinity of scTCR fusion proteins, particularly by increasing the off-rate. Conventional binding assays have been developed to study protein off-rates. In cases where the sequence of an antigenic peptide which specifically binds the scTCR is known or can be readily determined, the peptide can be mutagenized by, e.g., alanine scanning mutagenesis, to identify residues which specifically bind the CDR3 region of the scTCR. Binding between the mutagenized antigenic peptide and the scTCR can be evaluated by binding assays described herein. Accordingly, amino acid residues identified in the peptide will make it possible to identify contact residues in the scTCR molecule. Preferably, a

scTCR mutein produced by these methods will have the binding specificity of a TCR for antigen and the affinity of an antibody. One method of making the improved scTCR fusion proteins is by producing fusion protein muteins as described previously.

The improved scTCR fusion proteins can be made by isolating autoreactive scTCR fusion proteins using bacteriophage display libraries described in the examples which follow. The bacteriophage display libraries can then be used to pan against IA^s molecules covalently linked to peptides derived from PLP and MBP proteins. Once a scTCR is isolated, scTCR muteins can be made as described previously to further characterize peptide contact residues.

Example 14 - Production of Bacteriophage Display Libraries

The DNA vectors pKC46 and pKC51 described in Example 1, above, were used to display scTCR fusion proteins on the surface of bacteriophage after IPTG induction. The production of bacteriophage display libraries is generally well known and can be used to display polypeptides and proteins up to approximately 50 KD. See generally Smith, G.P. and Scott, J.K. in *Methods in Enzymology* (1993) 217:228.

Briefly, a flask containing 2x Luria Broth (LB) + 0.5% glucose and 100 µg/ml of ampicillin was inoculated with E. coli strain, XL1-B cells containing the plasmid vector pKC46 or pKC51. Following overnight growth, the cells were pelleted by centrifugation and resuspended in 2xLB without glucose. The cells were centrifuged again and washed a second time in 2xLB. After the final wash, cells were resuspended in 50 ml of 2xLB and IPTG was added to a final concentration of 1mM. The cells were grown for 2 hours at 37°C and then helper bacteriophage, VCSM13, was added at 10 pfu/ 5 ml of cell culture. After 15 minutes, the mixture of XL1-B cells and helper bacteriophage were diluted 1 to 50 into pre-warmed 2xLB containing tetracycline and ampicillin and 1mM IPTG. After an hour of growth at 37°C kanamycin was added to cultures to select for cells infected with helper bacteriophage. Cell cultures were grown overnight and bacteriophage were purified the next day after two rounds of PEG precipitation. To remove large debris from the sample, purified bacteriophage preparations were filtered through a 0.2 micron filter. Additionally, residual PEG was removed from the bacteriophage preparations by washing the sample in 1%FBS/PBS using

a 100 centricon membrane (100 mw cutoff). The bacteriophage titer was determined by counting colonies growing on plates. This is done by making 10-fold serial dilutions of bacteriophage and mixing the diluted samples with infection competent XL1-B cells and plating contents on 2xLB agar containing ampicillin. The bacteriophage titres were in the range of approximately 10^{10} to 10^{14} cfu/cell.

Following the second PEG precipitation, bacteriophage were sterilized by filtration through a 0.2 micron filter to remove undesirable particles and bacteria. The filtered preparation was then washed exhaustively using a centricon 100 (100 mw cutoff) filter to concentrate the bacteriophage and to buffer exchange into 1%FBS/PBS.

Example 15 - Characterization of Bacteriophage Libraries

A) ELISA Assay

A TCR specific ELISA assay was used to test for TCR molecules displayed on the surface of bacteriophage. Briefly, a 96 well plate was coated with neutrAvidin (Pierce) at 200 ng/well in coating buffer, pH 9.0 and incubated at 4°C overnight. The plate was blocked using 5% non-fat dry milk (NFDM) for one hour and then either anti-α,β TCR (H57) or anti-V-β8.2 (MR5-2) biotin labeled antibodies was diluted in 10 mM Tris, pH 8.0 containing 2.5% NFDM. The diluted antibodies were then individually added to the wells and incubated for one hour at RT. The plate was washed six times in TBS/Tween (0.5%) (TBST) to remove unbound antibody.

The bacteriophage-expressed fusion proteins were detected by incubating bacteriophage particles in wells coated with antibodies for one hr at RT. The plate is washed six times with TBST followed by the addition of anti-M13-HRP conjugate (Pharmacia) diluted in 2.5% NFDM. After a one hr incubation, the plate was washed eight times with TBST. 100 µl of TMB substrate was added to each well and after 10 minutes the reaction was quenched by the addition of 100 µl of 1M sulfuric acid. The plate was read at an absorbance OD of 450 nm (Fig. 17). We tested control bacteriophage (prepared from a CA III geneIII antibody library) for non-specific binding to antibodies H57 and MR5-2. Further controls were performed by assaying non-specific binding to wells coated w/BSA or with anti-V-β17.

Fig. 17 and Fig. 18 show an ELISA assay of scTCR fusion proteins under non-induced (ie. derepressed) and induced conditions. Fig. 17

illustrates scTCR fusion protein made from pCK46 and Fig. 18 shows fusion protein made from pCK51. In each figure, dark boxes show non-induced cultures and light boxes show induced cultures. Figures 17 and 18 show that scTCR fusion proteins were expressed in the bacteriophage library and displayed on the surface of the bacteriophages. The OD 450 nm absorbencies were approximately 60 to 200 fold higher in bacteriophage preparations induced to express scTCR fusion proteins than non-induced bacteriophage preparations (Fig. 18). The ELISA assay detected bacteriophage displaying gene VIII scTCR fusion proteins at approximately 200 to 500 fold higher levels than bacteriophage displaying gene III scTCR fusion (see Fig. 17). It is believed that the results indicate that the TCR/gene VIII bacteriophage have multiple scTCR fusion proteins expressed on the bacteriophage surface. Multivalent bacteriophage display of scTCR fusion proteins would improve chances of panning against MHC/peptide complexes because the multivalency would increase avidity.

B) Activity of Fusion Proteins Displayed in the Bacteriophage Library

To demonstrate that the fusion proteins on bacteriophage were biologically active, bacteriophage displaying the DO11.10 scTCR/gene VIII fusion were analyzed for the capacity to block specific interactions between the TCR on the DO11.10 T cells and an immobilized scIAd/OVA molecule. Exemplary assays to detect such interactions using a D011.10 T cell line and single-chain MHC molecules have been disclosed above.

A DO11.10 T cell hybridoma and IAd/OVA system was used in general accordance with the methods disclosed previously in Example 8 to measure the reduction of IL-2 levels in the presence of scTCR expressed on bacteriophage (sometimes referred to herein as "scTCR/bacteriophage molecules"). The experiments indicated that the bacteriophage-expressed scTCR fusion proteins interacted with immobilized Iad/OVA because IL-2 levels were reduced in wells that received scTCR/bacteriophage molecules. However, in wells incubated with equal titers of control bacteriophage (no displayed scTCR) a decrease in inhibition was not observed. Thus, the bacteriophage-expressed scTCR fusion proteins are biologically active.

To test the fine specificity of the inhibition, an assay was developed that compared the level of inhibition between DO11.10 and gD12 T

hybridomas. As disclosed previously in Example 8, gD12 T cell hybridomas are IA^d restricted but recognize a peptide derived from HSV-1. Because both cells recognize peptides restricted by IA^d, it is conceivable that the bacteriophage-expressed scTCR from D011.10 could have some interaction with the IA^d/HSV-1 molecule, although it is believed that this interaction would be substantially weaker than the interaction with IA^d/OVA MHC/peptide molecule. As shown in Fig. 19A, a low level of IL-2 inhibition was observed in the gD12 hybridoma group, however, the level of IL-2 inhibition in the DO11.10 group was approximately 8 to 10 fold greater. In Fig. 19A, approximately 8 to 250 X 10^{10} phage were used in each experiment. CA^{III} refers to a control phage with no displayed scTCR fusion protein. Fig. 19B shows the results of a related experiment in which IL-2 production was measured from D011.10T hybridoma cells.

C) BioPanning Fusion Proteins

Bacteriophage display libraries that present scTCR fusion proteins can be used to pan for specific TCR molecules in accordance with known methods (see e.g., McCafferty, J. et al. *Nature* (1990) 348:352; Castagroli, L. et al. *J. Mol. Biol.* (1991) 222:301; Lebeddee, S. L. et al. *PNAS* (USA) (1992), 89:3175; Smith, G.P. and Scott, J. K. *supra*; Blake, J. et al. *J. Exp. Med.* (1996) 184:121. Prior panning techniques generally rely on the strength of interactions between a target antigen and antibody which is typically in the range of 10^{-6} to 10^{-8}. However, most TCR-MHC/peptide interactions are weaker with KD values typically in the range of $5x10^{-5}$ M. In general, avidity and valency between scTCR fusion proteins and MHC/peptide complexes can be increased by increasing the number of fusion protein copies expressed on the phage. Other strategies which can be employed include changing wash stringency, increasing the amount of antigen, decreasing off-rate by lowering temperature, and increasing incubation time.

i) Antibody panning

Antibodies specific to the DO11.10 scTCR fusion protein were used to pan for scTCR molecules. Briefly, microtire wells were coated with 200ng of neutrAvidin followed by incubation with biotin labeled antibodies that bound to either the C-β domain, the V-β8.2 domain, or a non-specific antibody that recognized V-β17. Non-specific binding was also checked by use of wells coated with BSA. The experiments were conducted by diluting $2x10^6$

TCR/geneVIII bacteriophage particles into 1x10^{11} particles from an irrelevant antibody bacteriophage bank, thus a final dilution of 1:50,000 was done. A 5000 fold enrichment was observed after a single round of enrichment against both the anti-TCR antibody (H57) or the anti-V-β8.2 antibody (MR5-2). The BSA negative control did not yield any positive clones suggesting the enrichment was specific. A first round enrichment between 20 to 10000 fold is not uncommon in antibody antigen panning experiments, indicating that observed enrichment falls within an exceptable range of reported enrichment studies.

ii) Cell panning

Cell panning is a routine method of isolating antibodies against cell surface proteins. The method can be readily adapted to screen for desired fusion proteins in the bacteriophage library made in Example 18. Cells for use in cell panning can be from any suitable source, e.g., cells which express MHC/peptide molecules or cells which include an empty MHC complex to which a suitable peptide can be bound as disclosed in said pending U.S. Application Ser. No. 08/596,387. Additionally, cells can be employed that have been transfected with a single-chain class I or class II MHC gene in which a suitable peptide is bound or covalently linked to the MHC complex. Examples of cells with suitable single-chain class I or class II MHC/peptide complexes have been disclosed in said published PCT Application No. published PCT/US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387.

In general, panning with cells expressing a suitable MHC complex offers several advantages including promoting an available supply of such cells and avoiding time-consuming purification of the MHC/peptide complex.

In one cell panning method, approximately 10^{11} total bacteriophage with approximately 2 X 10^6 D011.10 bacteriophage can be mixed in an eppendorf tube (1.7 ml) with 10^6 cells in a volume of 0.2 ml for a two hour incubation at 4°C. Cells can then be pelleted by centrifugation at 5,000xg for 10 minutes at 4°C and washed 5 times in ice cold PBS/tween (0.5% w/v). Subsequently, bacteriophage can be eluted from the cells by adding 50 μl of citrate buffer, pH 5.0. The enriched bacteriophage population can be expanded by infecting E. coli and growing an overnight culture. Bacteriophage are then purified by standard procedures such as those

described previously in Example 14. After the 5th round of enrichment, a random sample of colonies can be picked and the genes sequenced. The frequency of DO11.10 TCR genes recovered will determine whether additional rounds of panning are required. For instance, it is expected that a 1:50000 initial dilution of DO11.10 TCR/bacteriophage would show an increase in frequency after five rounds of panning. The increase is expected to be in the range of approximately 1000 to 2000 fold.

iii) Panning With scMHC/peptide complexes

Soluble scMHC/peptide complexes can be made, e.g., in insect cells in accordance with methods previously described in said published PCT Application No. US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387.

Soluble scMHC/peptide molecules produced in insect cells can be used to pan for bacteriophage expressing soluble fusion proteins. For example, a concentration of scIA^d/OVA (e.g., 1 to 10 μg/well) can be used to coat 96 well plates (Nunc). Subsequently, $2x10^6$ DO11.10 bacteriophage can be diluted (1:50000) into 10^{11} total bacteriophage and incubated with immobilized IA^d/OVA. After a two hour incubation, the plate can be washed 5 times in TBST. Bound bacteriophage can be eluted by adding 100 μl of 0.1M HCl/glycine. The frequency of bound DO11.10 TCR/bacteriophage can be determined by performing standard colony lifts and screening for positives with an antibody against a protein tag (e.g., an anti-EE tag antibody as disclosed previously) or DNA specific probes, e.g., a labelled 300 bp α-chain DNA probe available from Amersham that recognizes the scTCR gene or gene product, respectively.

Example 16 - Fluorescence Assisted Cell Sorting Identification of Fusion Proteins

Fluorescence Assisted Cell Sorting (FACS) is a routine method for detecting and sorting cells (see e.g., Davey, H.M. and Kell, D.B in *Microbiological Reviews* (1996) 60:641; and Darzynkiewca, Z. et al. (1994) in *Flow Cytometry* 2nd Ed., Vols. 41 and 42 Academic Press, New York. FACS can be used to detect interactions between cells and bacteriophage displaying scTCR fusion proteins. To perform FACS experiments, cells expressing sc-IA^d/OVA complexes were made as disclosed previously. Staining with the IA^d specific antibody ASMII-FITC (Pharmingen) verified that

the cells expressed the IA^d. To confirm that the OVA peptide is present in the IA^d groove, a T cell activation assay can be perfomed as described in said published PCT Application No. published PCT/US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387.

A variety of chromagens can be used to label bacteriophages for FACS analysis. One approach is to couple bacteriophages with a suitable chromogen such as phycoerythrin. Another approach is to couple the bacteriophages with FITC in accordance with known methods such as those described in the Flurotag FITC conjugation kit (Sigma, St. Louis, MO). Still another approach is to couple phycoerythrin to bacteriophages indirectly by first biotinylating bacteriophages and coupling strepavidn-phycoerythrin thereto. Still another method would be to use a two antibody approach in which each antibody had a different fluoroscein tag. More particularly, an anti-bacteriophage antibody can be labeled with FITC and a second antibody to the scTCR (e.g., H57) can be labeled with phycoerythrin.

One bacteriophage coupling method is as follows: 10^{12} cfu of pKC51 phage are buffer exchanged into 0.1M sodium carbonate buffer (0.2ml) at a pH of between 9.0 and 9.5. Using the Flurotag FITC conjugation kit, one FITC vial is mixed in 1 ml of 0.1M carbonate-bicarbonate buffer and vortexed until all FITC has been dissolved. Approximately 50 µl of FITC label is added to the bacteriophage preparation so that the final ratio of FITC to phage is 40 to 1 to obtain a suitable fluroescein to protein (F/P) molar ratio. The sample is incubated for 2 hrs in a tube covered with aluminum foil. Labelled bacteriophage is isolated by applying the sample to a G-25 Sephadex column. Typically, the labelled bacteriophage will be in the main fraction (e.g., fractions 6 to 8). The F/P molar ration is subsequently determined using a spectrophotometer to read absorbance at 280nm and 495nm. An equation that can be used to determine the F/P molar ratio is the following:

$$\text{Molar F/P} = 2.77 \times A_{495} / A_{280}\ (0.35 \times A_{495})$$

The absorbance reading of the conjugate sample should suitably fall between 0.3 and 1.0.

The FITC labelled phage can be incubated with the cells expressing the sc-IA^d/OVA complex in accordance with conventional FACS methods to detect bacteriophage binding to the cells. Bound bacteriophage can be eluted from the cells and propagated in accordance with standard methods.

Example 17 - Cloning and Expression of scTCR Fusion Proteins in Bacteriophage f88

The panning methods described above employ phagemid-transformed cells co-infected with a wild-type filamentous bacteriophage (ie. VCMS13) to display scTCR fusion proteins. The methods can be improved by using bacteriophage vectors which more efficiently package recombinant scTCR constructs (ie. result in a higher yield of recombinant molecules per total number of virions). For example, bacteriophage f88-4 is a type 88 vector (9273 base pairs) that includes two gene VIII genes, one which is wild-type, and the other which displays a recombinant gene (ie. a gene VIII gene fusion). The bacteriophage f88-4 can be obtained from Dr. G. Smith of the University of Washington. The f88-4 bacteriophage packaged gene VIII constructs more efficiently, resulting in up to 10% increases in yield. It is believed that the increase in yield followed an increase in the multiplicity of recombinant virions (ie. number of recombinant virions per total number of virions). It is believed that the increase resulted in approximately 300 scTCR fusion proteins per virion. Thus, the f88-4 bacteriophage increased yield and multiplicity, and improved avidity of target binding thereby enhancing the probability of isolating specific scTCR fusion proteins.

Recombinant bacteriophages including scTCR fusion proteins were constructed by cloning an scTCR gene into the PstI and HindIII sites of the f88-4 bacteriophage. Expression of the inserted scTCR gene is thus under the control of the tac promoter and induction occurs after the addition of 1mM IPTG.

Fig. 20 schematically illustrates several recombinant bacteriophage vectors made using the f88-4 bacteriophage (pKC70, pKC71, and pKC72).

Example 18 - Construction of scTCR Bacteriophage Libraries from HIV-infected Cells

A bacteriophage library displaying scTCR fusion molecules derived from CTLs of HIV-infected patients can be made in accordance with the methods described herein. HIV-infected patients to be used are those who have been diagnosed or categorized as long-term non-progressors (ie. LTNP). These HIV-infected patients have been studied for CTL responses to various HIV antigens including gag and pol. CTL profiles from the patients typically show strong immunoactivity to HIV antigens in comparison to patients who

are susceptible to AIDS. See generally Miedema, F. and Klein, M.R. *Science* (1996) 272, 505.

To identify TCRs participating in the CTL response and to construct corresponding fusion proteins, a class I HLA-A2 restricted human TCR library can be made from T cells isolated from the LTNP patients in accordance with the examples described above.

Several methods can be employed to prepare the class I HLA-A2 restricted bacteriophage library. For example, one way is to isolate and pool 10^7 T cells from three HLA-A2 LTNP patients as described previously (see Altman, J.D. et al. *Science* (1996) 274:94). Messenger RNA can be purified from these cells and cDNA made by standard procedures such as by using an oligonucleotide primer to human C-α and C-β TCRs. Exemplary primers are disclosed in Fig. 22 (SEQ ID NOs: 116 to 128) and Fig. 23 (SEQ ID NOs.: 101-115). More specifically, the V-α genes can be PCR-amplified using 12 forward primers (Fig. 22 SEQ ID NO. 116-127) and a single back primer (SEQ ID NO.: 128) that hybridizes at the 5' end of the C-α gene sequence. The β chain can be PCR-amplified by using 13 forward primers (Fig. 23, SEQ ID NOs: 101-113) that hybridize at the 5' end of V-β chain and two back primers (Fig. 23 SEQ ID NOs: 114, 115) situated 378 bases into the β constant domain. The PCR amplification can be performed in accordance with standard methods.

The PCR-amplified DNA can be inserted into suitable DNA vectors that a bacteriophage coat protein or fragment thereof such as those disclosed in Example 14. More particularly, the pKC45 DNA vector discribed in Example 2 can be used to subclone V-α chains into the SfiI and SpeI of the vector, and the V-β/C-β chains can be cloned into the XmaI site therein. A suitable vector encoding the scTCR bacteriophage fusion protein can then be made in accordance with the above examples. Alternatively, the V-α chains, and V-β/C-β chains can be subcloned into the f-88 bacteriophage vector (see Example 17), e.g., as an insertable HindIII to PSTI fragment. The recombinant bacteriophages thus produced can be used to infect suitable host cells and to propagate and screen recombinant bacteriophage in accordance with examples disclosed previously.

In some cases, it may be desirable to modify cloning sites of the f88 bacteriophage in accordance with standard recombinant techniques to

permit cloning of the particular fragments (e.g., an SfiI-XmaI fragment) such as by including suitable linker sequences. The modification can be accomplished, e.g., by annealing suitable restriction site primers into HindIII and PstI sites of the bacteriophage. The bacteriophage display library thus produced can be amplified and stored in accordance with standard procedures.

Example 19 - Screening Bacteriophage Display Libraries from HIV-infected Cells

The recombinant bacteriophage library produced in Example 18 can be screened by several alternative approaches. For example, the library can be screened with a variety of detectably-labelled probes including whole (inactivated) HIV virus, HIV proteins, particularly HIV coat proteins, and APCs expressing HIV peptides in the context of an MHC/HLA complex. The screen can be conducted with a peptide epitope of an HIV coat protein which is known to stimulate an immune response against the HIV virus *in vivo*. Several examples of such peptide epitopes are known and include peptides isolated from the HIV gp120, gp41, gp160, gag and pol coat proteins.

a) Screening with HIV gp120 coat proteins

Peptide epitopes from the V3 loop of the gp120 protein can be used to screen the bacteriophage library. Exemplary peptides include the T1 (amino acids 428-443) and T2 (amino acids 112-124) peptides of the HIV gp120 protein. Peptide epitopes from the gp120 V3 loop are among those capable of inducing HIV neutralizing antibodies (see Berzofsky, J. A. et al. (1991) *FASEB J.* 5:2412; Ahlers, J.D. et al, (1993) *J. Immunology* 150:5647). See also Karzon, D.T. et al. and Hart, J.K. et al. for examples of other peptide epitopes which can be used to screen the bacteriophage library for scTCR fusion proteins (Karzon, D.T. et al. (1992) *Vaccine* 14:1039; Hart, J.K et al. *PNAS* (USA) (1991) 88:9448).

B. Biopanning With APCs Expressing HIV Coat Proteins

The scTCR library constructed in Example 18, above, can be panned for scTCR fusion proteins which bind immunogenic HIV peptides such as those derived from the HIV gag or pol protein. Thee HIV coat proteins are presented in the context of cells expressing single-chain HLA-A2 molecules. The single-chain HLA-A2 molecules are made as described in Garboczi, D.N.

et al. *PNAS* (USA) (1992) 89:3429. Cells expressing the single chain HLA-A2 molecules can be made in accordance with known methods (Altman, J.D. et al., *supra*).

Biopanning can be accomplished by several methods. For example, one way is to use two different presentations of the MHC/peptide target. An initial round of panning will use transfected cells expressing HLA-2 and either gag or pol peptides as a target antigen. Panning is performed by using approximately 10^{11} bacteriophage from the bacteriophage display library described in Example 18. The bacteriophage library is then contacted with cells presenting the HLA-A2 and gag or pol peptide. Bacteriophage can be incubated with approximately 10^{6} transfectants for two hours at 4°C, washed 2 times in 2%FBS/PBS and then eluted in 100 µl of 0.1M citrate buffer, pH 5.0 and neutralized with 10 µl of 0.1M Tris, pH 8.0. Eluted bacteriophage can be propagated by infecting a suitable host such as E. coli strain K91kan, and growing bacteriophage overnight. Bacteriophage particles can be purified by standard procedures.

Multiple rounds of panning against the cells or a solid support bearing a suitable MHC/antigen can increase the purity of bacteriophages bearing the scTCR fusion proteins identified in the cell panning experiment. For example, the bacteriophages isolated by the cell panning method can be purified by panning against a solid support (e.g., a microtitre dish) coated with single chain HLA-A2 and peptide. After a two hour incubation, non-specific bacteriophage can be removed by washing wells about 8x with 0.3 ml of PBS/0.2% Tween. Bound bacteriophage can be eluted in 0.1 ml of 0.1M HCl in glycine, pH3.0 and neutralized in 10 µl of 2M Tris, pH8.0. Additional panning can be performed by alternating between use of cells and immobilized MHC/HLA peptide molecules. After approximately 5 or 6 rounds of panning, a substantially pure preparation of bacteriophage displaying scTCR will result. Subsequently, DNA can be isolated from the bacteriophages to determine the DNA sequence of the α and β variable domains of the scTCR encoded by the bacteriophages. It is expected that a bias or enrichment in the frequency of α or β variable domain usage is indicative of a productive interaction between a scTCR in the bacteriophage display library and an MHC/peptide antigen.

The detectably-labelled probe will be used to enrich the bacteriophage library for a recombinant bacteriophage of interest. For example, when the probe is a peptide epitope from the gp120 V3 loop, recombinant bacteriophages can be isolated which specifically bind the peptide. Typically, several enrichment steps will be performed in which the number of steps will depend on several factors such as, e.g., representation of the desired recombinant bacteriophage in the library, or avidity of the detectably-labelled probe. DNA from the recombinant bacteriophage will be isolated by standard means. DNA encoding the scTCR fusion protein will then be sequenced in accordance with standard methods. DNA sequencing of several recombinant bacteriophage isolates will be indicative of specific binding between the detectably-labelled probe and the scTCR fusion protein encoded by the recombinant bacteriophage.

High frequency clones will then be expressed as soluble and fully functional scTCR fusion proteins in suitable vectors such as the pKC60 and pKC62 vectors described previously. The expressed fusion proteins can then be individually purified if desired by immunoaffinity chromatography using the previously described H57 monoclonal antibody in accordance with standard methods.

Example 20 - Characterization of scTCR Fusion Proteins Detected by Anti-HIV Panning

Several alternative methods can be used to evaluate specific binding between the recombinant bacteriophage detected above and HIV antigen.

A) BioCore Analysis

In cases where an HIV peptide was used to screen the bacteriophage library described above in Example 18, the peptide can be used to make a scMHC class I molecule in accordance with methods described in published PCT Application No. published PCT/US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387. Preferably, the peptide will be covalently linked to the scMHC class I molecule. The scMHC class I peptide complex can then be used to coat chips for BioCore Analysis as described below in Examples 7 and 20. More specifically, single chain HLA-A2 molecules bound with gag or pol antigen (see Altman, J.D. et al. supra) can be covalently coupled through amine reactive

sites to the biosensor chip. The chip is then contacted with a sample including the scTCR fusion protein. Specific binding can be detected on the chip by described above. See also Seth, A. et al. *Nature* (1994) 369:324; Matsui, K. et al. *PNAS* (USA) (1994) 91:12862). It is expected that most scTCR fusion protein interactions will be in the range of 10^{-5} to 10^{-7}M.

Detection of specific binding between the scMHC class I peptide complex and the scTCR fusion protein would indicate presence of a specific scTCR-peptide binding complex.

By determining a binding coefficient for each of the isolated scTCR fusion proteins the effectiveness of the receptor for binding and triggering cell death can be readily predicted.

B) Binding to scTCR Fusion Protein Tetramers

Specific binding between scTCR fusion proteins and an HIV peptide can also be detected by assaying binding with scTCR fusion protein tetramers in accordance with examples described above (see Example 9). Tetrameric scTCR fusion protein can also be made by inserting DNA encoding the fusion in a suitable DNA vector which includes a Bir A-dependent biotinylation site (see Schatz, P.J. *Biotechnology* (1993) 11:1138). The scTCR fusion proteins can be further modified by adding avidin-phycoerythrin in accordance with standard methods to produce the tetrameric scTCR fusion proteins. Transfected cells which display the HIV peptide can be prepared as described above and in accordance with methods described in published PCT Application No. published PCT/US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387. The transfected cells can be used to screen the library and can be stained with the labelled scTCR fusion protein tetramer to detect specific binding to the cells. Stronger binding by FACS analysis would be indicative of a specific interaction of the scTCR fusion protein with the MHC class I peptide complex.

The scTCR fusion proteins isolated in Example 19, above, can be tested for binding affinity and activity to determine if the scTCR fusion proteins specifically bind the MHC/peptide complex. Examples of such suitable assays are those described in the examples above.

C. FACS Analysis

FACS can be used to detect interactions between the scTCR fusion proteins and target cells discussed in Example 16, above. For example, the scTCR fusion protein can be biotinylated in accordance with standard methods and combined with strepavidin-phycoerythrin to form labelled sc-TCR tetramers. FACS can be used to qualitatively measure the interaction of the scTCR and a suitable target cell such as A20 cells and tumor cell lines. Alternatively, FACS can be conducted by coupling the scTCR fusion proteins of Example 16 to a suitable solid support (e.g., latex beads) to display multiple copies of the scTCR. A related method has been shown to produce tetrameric class I MHC/peptide molecules (see e.g., Altman, J.D. et al. *supra*).

D. Il- Expression in gD12 T hybridoma cells

Activation of gD12 T hybridoma cells can be readily assayed by measuring IL-2 activity as disclosed previously in said pending U.S. Patent Application Ser. 08/596,387. This assay can be used to assess the function of the scTCR fusion proteins produced in Example 16. For example, gD12 T hybridoma cells can be transfected with DNA encoding a scTCR molecule produced in Example in accordance with methods disclosed previously. FACS staining can be conducted as disclosed in Example 16 to detect scTCR receptor expression on the cell surface. Receptor positive clones can be used in the IL-2 activation assay described in said published PCT Application No. PCT/US95/09816, as well as said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387. If the scTCR receptor is active (ie. it specifically binds the MHC/peptide target), Il-2 production from the gD12 cells can be readily detected and measured.

Example 21 -Isolation of Autoimmune Protein Fusions Binding Class II Restricted MHC/peptide complexes

The present methods can be used to isolate scTCR fusion proteins which specifically bind autoimmune proteins and peptides. For example, T cells can be isolated in accordance with conventional methods from individuals that are DR-2+ and have been diagnosed with multiple sclerosis. TCR DNA can be obtained from the T cells and used to construct a scTCR fusion proteins in accordance with methods described in the examples above. The bacteriophage display library can be made and tested in accordance with Examples 14-15, above.

The bacteriophage display library can be made by isolating 10^7 T cells from several DR-2+ patients with multiple sclerosis. T cell mRNA can be purified and cDNA made as described in Example 1, above. PCR amplification of the TCR V-α and V-β/C-β chains can be performed by using the same primer set as described in Example 1. The V-α and V-β/C-β chains can be cloned into cloning sites of suitable bacteriophage display vectors such the SfiI-SpeI and XhoI-XmaI sites, respectively, of the f88-4 bacteriophage vector DNA disclosed in Example 17, above. The library can be amplified and stored according to standard methods to pan specific antigenic targets.

The single-chain DR-2 molecules are made in general accordance with methods described above, in said published PCT Application No. PCT/US95/09816, said pending U.S. Patent Application Ser. Nos. 08/382,454 and 08/596,387, as well as Rhode, P. et al. *J. of Mol. Immunology*, (1996) 32, 555 . More specifically, HLA-DR2 molecules can be purified from EBV transformed lymphoblastoid cells which present the HLA-DR2 molecule. Briefly, the HLA-DR2 molecule can be purified by standard immunoaffinity chromatography by solubilizing the cells with buffer including Triton X-100. The cell lysate is then applied to an antibody-Sepharose column. DR2 is bound and eluted in phosphate buffer containing 0.05% N-dodecyl B-D-maltoside detergent at pH 11.3. Fractions are immediately neutralized with 1M acetic acid and the DR2 pool is collected through a DEAE ion exchange column in phosphate containing 0.5M NaCl pH 8.0. The protein fraction can be assayed for purity by SDS-PAGE gel electrophoresis followed by silver staining.

The bacteriophage library can be screened by several methods, particularly panning against a solid support coated with the single-chain DR-2 molecule in accordance with methods described previously. The panning can be conducted by producing single-chain DR-2 molecules in a host such as insect cells and immobilizing the single-chain DR-2 molecules on a solid support such as walls of a microtitre plate.

Additionally, the bacteriophage library can be purified with cells that have been transfected with DR-2 molecules (see DeKruif, J. et al. *PNAS* (USA) (1995) 92, 3938. Enrichment for bacteriophage particles expressing

scTCR fusion proteins which specifically bind the DR-2 protein can be performed as described above in the above examples.

The invention has been described with reference to preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of this disclosure, may make modifications and improvements within the spirit and scope of the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION

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(ii) TITLE OF THE INVENTION: FUSION PROTEINS COMPRISING BACTERIOPHAGE COAT PROTEIN

(iii) NUMBER OF SEQUENCES: 130

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ Version 1.5

(vi) CURRENT APPLICATION DATA:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGGCCATGGC CCAGCTGCAG ACTAGTGC 28

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GGCCGCACTA GTCTGCAGCT GGGCCATGGC CGGCT 35

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTCGCGGCCC AGCCGGCCAT GGCCGAGGCT GCAGTCACCC AAAGC 45

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CTTCCTCACT AGTACAGTCT GCTCGGCCCC AG 32

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GATGGCCTCG AGGAGCAGGT GGAGCAGCTT 30

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GACTAGCCCG GGACAGGGAA CGTCTGAACT GGG 33

(2) INFORMATION FOR SEQ ID NO:7:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTCGCGGCCC AGCCGGCCAT GGCCGAGCAG GTGGAGCAGC TTCCT 45

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CTCGCGCTCG AGGAGGCTGC AGTCACCCAA AGC 33

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO

(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTCGCGCCCG GGACAGTCTG CTCGGCCCCA GGC 33

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTCGCGACTA GTACAGGGAA CGTCTGAACT GGG 33

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CTCGCGCCCG GGGTCTGCTC GGCCCCAGGC 30

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CTCGCGACTA GTGGGAACGT CTGAACTGGG 30

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTCGCGACTA GTGTCTGCTC GGCCCCAGGC 30

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCGCGCCCG GGGGGAACGT CTGAACTGGG 30

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CTCGCGCTCG AGCGAGGCTG CAGTCACCCA AAGC 34

(2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GGGGGGCCCG GGGCTGAGGG TGACGATCCC GCAAAAG 37

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 67 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CTAGTCTGGT GGCGGTGGCA GCGGCGGTGG TGGTTCCGGT GGCGGCGGTT CTGGCGGTGG 60
CGGTTCC 67

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 67 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

TCGAGGAACC GCCACCGCCA GAACCGCCGC CACCGGAACC ACCACCGCCG CTGCCACCGC 60
CACCAGA 67

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GTGCTCACTA GTGTTTGGCT CTACAGTGAG TTTGGTG 37

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GATGGCTCGA GTGAGCAGGT GGAGCAGCTT CCT 33

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CTAGTCCCCG GGTACAACTG TGAGTCTGGT TCC 33

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CTCGAGACTA GTTACAACTG TGAGTCTGGT TCC 33

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CGGCCGAGGA AGAAGAGTAC ATCCCGATGG ATC 33

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO

(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GGGCCATCCA TCGGGATGTA CTCTTCTTCC TCGGCCGGCT 40

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CCGGGGAGGA AGAAGAGTAC ATCCCGATGG ATTGAG 36

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AATTCTCAAT CCATCGGGAT GTACTCTTCT TCCTCC 36

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GCCCGGGACT AGTGC 15

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGCCGCACTA GTCCCGGGCT GCA 23

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

CTAGTCCCCG GGTCATCAAG CGGCGCCTTC CATCGGCATG TACTCTTCTT CCTCTACAAC 60
TGTGAGTCTG GTTCC 75

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

CTAGTCCCCG GGTCATCAAG CGGCGCCTTC CATCGGCATG TACTCTTCTT CCTCGTCTGC 60
TCGGCCCCAG GC 72

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CTAGTCCCCG GGTACAACTG TGAGTCTGGT TCC 33

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CCGGGGAGGA AGAAGAGTAC ATGCCGATGG AAGGCGCCGC TTAGC 45

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CCTCCTTCTT CTCATGTACG GCTACCTTCC GCGGCGAATC GGGCC 45

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GATCAGCCCG GGGAGGCTGC AGTCACCCAA AGC 33

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CTAGTCCCCG GGACAGTCTG CTCGGCCCCA CCG 33

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CCGGGGAGGA AGAAGAGTAC ATGCCGATGG AAGGCGCCGC TC 42

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CCTCCTTCTT CTCATGTACG GCTACCTTCC GCGGCGAGGG CC 42

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CGCCGCTCAC CATCACCATC ATCACTGATG AC 32

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GGCGAGTGGT AGTGGTAGTA GTGACTACTG GGCC 34

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GATCAGGGCG CCGCTACTGT TGAAAGTTGT TTA 33

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CTGATCGGAT CCTCATTAAA GCCAGAATGG AAA 33

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CCGGGCTAAG CGGCGCCTTC CATCGGCATG TACTCTTCTT CCTCC 45

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CCGGGAGCGG CGCCTTCCAT CGGCATGTAC TCTTCTTCCT CC 42

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CCGGGTCATC AGTGATGATG GTGAGCG G 35

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GCTCGAGCTT ACTCC 15

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGCTCATTAG GCGG 14

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GTGTACTTCT GTGCC 15

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CTGTGAGTCT GGTTC 15

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GCAGGTTCTG GGTTC 15

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CATTTACTAA CGTCTGG 17

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGCCTGGTAC TGAGC 15

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CCTCAACCTC CTGTC 15

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CTTATTCCGT GGTGTC 16

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CCACCCTCAG AACCG 15

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GAATTTACCG TTCCAG 16

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

CTTTAGCGTC AGACTG 16

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GAAACGCAAA GACACC 16

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGGGGGCCCG GGCTGCTGAG GGTGACGATC CCGCAAAAG 39

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GGGGGGGAAT TCTATTAGCT TGCTTTCGAG GTGAATTTC 39

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GAGCACGGCC CAGCCGGCCA TGGCCGAGGC TGCAGTCACC C 41

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GAGCACGAGA CTAGTAGCAC GAACAACACG GTCGTCGATC GGTTCCGGCG GGTTTGGCTC 60
TACAGTGAG 69

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

GATCCCTCCT GGACACGCAG GATGGAAGGA AGCTGCTCCA CCTGCTCAGC ACGAACAACA 60
CGGTCGTCGA TCGGTTCCGG CGGGGC 86

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CATGGCCCCG CCGGAACCGA TCGACGACCG TGTTGTTCGT GCTGAGCAGG TGGAGCAGCT 60
TCCTCCCATC CTGCGTGTCC AGGAGG 86

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GAGGTGGAAT TCTATTAAGA CTCCTTATTA CGCAGTATG 39

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GAGGAGGTGG TGACTAGTAG CAGGTTCTGG TGGGTTCTGG ATGTTTGGCT CTACAGTGAG 60

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GAGGAGGTGG TGACTAGAAG CAGGTTCTGG GTTCTGGATG TTTGGCTCTA CAGTGAG 57

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GAGGTGGAAT TCTATTAGTG ATGATGGTGA TGGTGAGACT CCTTATTACG C 51

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GAGGTGCCCG GGACTGTTGA AAGTTGTTTA GC 32

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

GAGGTGGAAT TCTATTAGTG ATGATGGTGA TGGTGGCTTG CTTTCGAGG 49

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GAGGTGGAAT TCTATTAGCT TGCTTTCGAG G 31

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

GAGGTGCCCG GGGCTGAGGG TGACGATCCC G 31

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

AATTCTCATC AGTGATGATG GTGATGGTGC 30

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

CCGGGCACCA TCACCATCAT CACTGATGAG 30

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GTGGAGCCCG GGTTCCATCG GCATGTACTC TTCTTCCTCT ACAACTGTGA GTCTGG 56

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 64 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

GAGGTGGAAT TCTCACCCGG GTTCCATCGG CATGTACTCT TCTTCCTCGT CTGCTCGGCC 60
CCAG 64

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GAGGTGCTGC AGGTTCCATC GGCATGTACT CTTCTTCCTC GTCTAGACGG CCCCAGGCCT 60
C 61

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

GTGGAGCTGC AGGGTCTAGA CGGCCCCAGG CCTC 34

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

GTGGAGCTGC AGGTGATCCA CCCCCTCCAG ATCCACCCCC TCCGTCTGCT CGGCCCCAG 59

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GTGGAGAAGC TTTGCCGAGC AGGTGGAGCA GC 32

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GGGGGGGAGG TGCTGGAGCG AGGCAGCAGT CACC 34

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GAGCCCACTA GTTTGGCTCT ACAGTGAGTT TGGTG 35

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CTAGACCAGC AAATCTGCAC CCACAGAATC CCTAGGACAG CTCCCAGGTT CCTCTGCATG 60
GTGGA 65

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

AGCTTCCACC ATGCAGAGGA ACCTGGGAGC TGTCCTAGGG ATTCTGTGGG TGCAGATTTG 60
CTGGT 65

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

GATCGGTCTA GAGGTGAGCA GGTGGAGCAG CTTCC 35

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

GCCTGGAGAC TCAGCCATG 19

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

GAAGTACATG GCTGAGTCTC C 21

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GATGAACGTT CCAGATTCCA TGG 23

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

CCCAAATCAA TGTGCCGAAA AC 22

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

CTAGAACACA GGAGACTGGA GAGCACGAAG AAGAGCCTGG AGCCCATGGT GGA 53

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

GCTCTCCTTG TAGGCCTGAG 20

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

GTACTTCTGT GCCAGCGGTG 20

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

GAGCAATTAT AGCTACTGCC TG 22

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

GGTCTGGAGG CCTTGTATCC 20

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

AGCTTCCACC ATGGGCTCCA GGCTCTTCTT CGTGCTCTCC AGTCTCCTGT GTT 53

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

TCGAGGAACC GCCACCGCCA GAACCGCCGC CACCGGAACC ACCACCGCCG CTGCCACCGC 60
CACCA 65

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CTAGTGGTGG CGGTGGCAGC GGCGGTGGTG GTTCCGGTGG CGGCGGTTCT GGCGGTGGCG 60
GTTCC 65

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

CCACCATG 8

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: N-terminal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
Glu Glu Glu Glu Tyr Met Pro Met Glu
 1               5
```

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

```
ATGAAATACC TGCTGCCGAC CGCAGCTGCT GGTCTGCTGC TGCTGGCGGC CCAGCCGATG      60
GCC                                                                    63
```

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: N-terminal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

```
Met Lys Tyr Leu Leu Pro Thr Ala Ala Ala Leu Leu Leu Leu Ala Ala
 1               5                  10                  15
Gln Pro Ala Met
            20
```

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
GCCGGCCATG GCCRGTGCTG TCRTCTCTC                                        30
```

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

GCCGGCCATG GCCGAMRCCM ARGTSACCC 29

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GCCGGCCATG GCCGATGTGA AAGTAACCC 29

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

GCCGGCCATG GCCGAMRCWG MCRTYTMCC 29

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE: